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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/837,235	04/18/2001	Christopher P. Marshall	9725-005	1399

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EXAMINER	
SAIDHA, TEKCHAND	
ART UNIT	**PAPER NUMBER**
1652	15

DATE MAILED: 08/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/837,235	MARSHALL ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/07/03 (Paper No. 14).* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-20 and 22 (14 & 17 in-part)* is/are pending in the application.

4a) Of the above claim(s) *1-9, 21 (14 & 17 in-part)* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-20 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. The Preliminary Amendment filed April 30, 2002 has been entered.

2. ***Election***

Applicant's election of Group II in Paper No. 14 (claims 10-13, 14 (in-part), 17 (in-part), 15-16, 18-20 & 22 is acknowledged. **Because applicant did not distinctly and specifically point out** the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Applicants drawing submitted in this application has been approved by the Draftsman.

4. **Claims withdrawn** :

Claims 1-9, 14 (in-part), 17 (in-part), & 21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 4.

5. ***Specification***

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

6. Claims 14 & 17 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 14 & 17 are objected to for depending upon non-elected claims.

Claim Rejections - 35 USC § 112 (first paragraph)

7. Claims 10-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated stabilized protein, comprising isolating a polypeptide, selecting one or more tyrosine residue pairs in a polypeptide chain, cross-linking the tyrosine residue pair(s) under defined conditions, does not reasonably provide enablement for any isolated protein comprising a di-tyrosine cross-link by genetic engineering. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 10-17 are drawn to 'an isolated protein comprising at least one di-tyrosine cross-link' introduced by genetic engineering.

While recombinant and mutagenesis techniques are known, it is not routine or known in the art or enabled in the instant specification to introduce a di-tyrosine cross-link by genetic engineering. Genetic modification of the protein structure to introduce or substitute an amino acid with a tyrosine is well known (example – Brown et al. (1998) in a peptide chain. Cross-linking of tyrosine residues has been achieved by chemical methods and under defined conditions such as in the presence of oxidants : oxone and monoperoxyphthalic acid (MMPP). However genetic expression of tyrosyl-tyrosyl cross-linked protein remains unknown and therefore claims to recombinantly produced cross-linked protein(s) or compositions thereof are not enabled.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of

enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the production of recombinant cross-linking having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue in using the modified enzyme in the method claimed. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

8. ***Pharmaceutical composition***

Claims 14-16 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to an isolated cross-linked polypeptide having catalytic or binding activity.

Factors to be considered in determining whether undue experimentation is required, are summarized in *re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) [*Ex parte* Forman [230 USPQ 546 (Bd. Pat. App. & Int. 1986)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

It is neither taught nor any data is provided for using the cross-linked polypeptide in pharmaceutical compositions for the treatment of any of the diseases or disorders. There is no evidence presented that cross-linked polypeptide is associated with any of the known diseases or disorders or can be treated by administering the cross-linked polypeptide. Without such a data or evidence, claims to pharmaceutical composition comprising cross-linked polypeptide would amount to a composition or potential drug for treatment for any disorder or disease, which is not enabled. Given the lack of direction or guidance and the nature of the invention, obtaining such a composition for one of skill in the art would be highly unpredictable. This is because the polypeptide when associated with a particular disease or disorder would be expressed

differentially. Manipulating or controlling these levels depends upon the disease or disorder, and may not always be controlled by supplementing with such a polypeptide composition. Further, no guidance in provided, pertaining to the fate of the administrated polypeptide in vivo.

Since it is not routine in the art to engage in *de novo* experimentation to prepare numerous compositions where the expectation "of success is unpredictable", the skilled artisan would require additional guidance, specific to individual disorder or disease, in order to make and use pharmaceutical compositions in a manner reasonably commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

9. ***Claim Rejections - 35 USC § 112*** (second paragraph)

Claims 10-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10, lines 1-2, recite 'cross-link introduced by genetic engineering'. The claim is indefinite because such a cross-link cannot be introduced by genetic means.

Claims 11-17 are included in the rejection for failing to correct the defect present in the base claim(s).

10. For the purposes of examining and in view of the unclear meaning of the phrase or the limitation 'cross-link introduced by genetic engineering', when given the broadest interpretation has been considered here to carry no patentable weight, and the claims are examined to mean cross-linking obtained by chemical means.

11. ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 10, 12, 17-19 & 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Aeschbach et al. (1976), BBA 439, 292-302 (AA – IDS). Aeschbach et al. teach a method for formation of Dityrosine cross-links in proteins, the hormone insulin for example, by oxidation using hydrogen peroxide. The reference teaches all the claim limitations, is therefore anticipatory.

12. Claims 10-13, 17-20 & 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. [Biochemistry, 1998, 37 : 4397-4406, **AD** - IDS]. Brown et al. teach protein-protein cross linking to be mediated by Ni(II) complex of the tripeptide gly-gly-his fusion protein, target being tyrosine, in the presence of oxidants such as oxone and monoperoxyphthalic acid (MMPP) and method of making the cross-linked peptide. Cross-linking has been achieved for small peptides, ecotin or GGH-ecotin cross-linked to a serine protease. The cross-linking methodology

allows for the protein cross-linking reagent to be encoded at the DNA level, thus circumventing the need for post-translational modification (see Abstract and Results and Discussion), **even though the crossing linking is still oxidative. PCR**-mutagenesis was performed to change ecotin Asp-137 to a tyrosine. The GGH-ecotin D137Y was subjected to same cross-linking conditions with no change in the binding affinity (see page 4402, column 2, 1st paragraph).

13. Applicants' Information Disclosure Statement (IDS) reference numbers - AI, AJ, AK, AN, AQ & AW are other potential references – but have not been used in any art rejection – in order to limit the number of issues while using the best art.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Tekchand Saidha
Primary Examiner, Art Unit 1652
August 5, 2003